Haptic Rendering Algorithm for Biomolecular Docking with Torque Force

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Abstract—Haptic devices enable the user to manipulate the molecules and feel interactions during the docking process in virtual environment on the computer. Implementation of torque feedback allows the user to have more realistic experience during force simulation and find the optimum docking positions faster. In this paper, we propose a haptic rendering algorithm for biomolecular docking with torque force. It enables the user to experience six degree-of-freedom (DOF) haptic manipulation in docking process. The linear smoothing method was proposed to improve stability of the haptic rendering during molecular docking.

Keywords—haptic rendering; biomolecular docking; torque feedback;

I. INTRODUCTION

Cyberworlds can integrate visual, audio and haptic tools both for research and e-learning. Biomolecular docking is a new research area which includes development of software system with both visual and haptic interfaces for rational drug design. In previous papers [1-2], we proposed a visual haptic-based biomolecular docking system for helix-helix docking research and implemented the application of this system in e-learning. In this paper, we propose an improved haptic rendering algorithm for biomolecular docking with torque force. The user can experience 6-DOF haptic force-torque feedback during the process of molecular docking.

The molecular docking process of drug design can be simulated in a three-dimensional space where a ligand can be docked onto a receptor. By using computer-aided design system, the manipulation of molecules can be realized with real-time interactive visualization in virtual environment. Especially, it has been proved to be very helpful for users to understand the interactions between molecules in e-learning applications.

On the other hand, a haptic interface appears to be another feasible way to improve the immersion and interaction during the molecular docking process in virtual environment. Haptic technology provides interactivity between real and virtual environment through force feedbacks transmitted by the haptic devices. This makes possible to manipulate molecules and transform biomolecular interactions into sensory experiences during a virtual experiment. Therefore, haptic-based visual biomolecular docking allows developing more interactive systems that could be used in rational drug design and molecular medicine.

Biomolecular docking is an assembling process for molecular structures to predict the preferred complimentary molecular shapes that can bind molecules to form a stable complex. Since there is an exponential increase in conformations as the number of atoms increases, the simulation of docking task with an automatic conformation search algorithms could be difficult. By using visual haptic-based molecular docking system, the user can manually explore the conformational molecular space to find an optimal conformation within the minimum time.

Some previous studies have proved that the force display can provide a better understanding of the molecular docking process compared with traditional visual display methods [3]. Because haptic device provides realistic force feedbacks to the users, in recent years, more and more researchers tend to explore and analyze the molecular docking process with haptic interface [4-6].

In earlier work [7], Ouh-young proposed a real-time system for interactive molecular docking that allows the user to manipulate the position of ligand and feel the interactive forces between molecules. A force smoothing method has been presented in [8] where forces from the Lennard-Jones (LJ) force field were calculated and the instability was eliminated when two atoms are in contact.

Besides traditional 3-DOF haptic force feedback, the torque force also plays an important role in molecular docking process. Persson and Cooper [9] developed a force-torque haptic molecular interaction system. They also conducted an evaluation to test an importance of force feedback in learning and understanding the interactions between molecules. The results proved that both force and torque forces play important roles in helping students to understand the concepts of molecular interaction. In [10], a 5-DOF haptic device and computational engine were developed for computer-aided molecular docking (CAMD) which provided both force and torque feedback.

This paper is organized as follows. Section II introduces the research background in biomolecular docking. Section III describes basic concepts of our haptic rendering algorithm and the method that we used to improve the stability of haptic force and torque display. Simulation results and analysis are given in section IV. In Section V, conclusion and future work are discussed.
II. RELATED WORK

Modern molecular visualization systems such as RasMol [11], PyMol [12], J Mol [13], MDVQS [14], etc allow visualize and analyze complex molecular structures. On the other hand, haptic-based technology allows molecular docking with force feedback in such way that the user could “feel” force field of bimolecular interactions. There are haptic-based systems that also enable users to feel an electrostatic force of the explored molecule.

Lai-Yuen and Lee [15] developed a computer-aided design system with the lab-built 5DOF haptic device for molecular docking and nanoscale assembly. Nagata and Mizushima [16] developed a prototype for protein-ligand docking simulation with the total potential energy (Van der Waals potential energy, electrostatic potential energy and hydrogen bond potential energy) calculation between atoms of ligand and protein. In [17], a grid map was used to generate the electrostatic field data around the molecular structure. The haptic forces at any position were calculated using tri-linear interpolation of the potential energy. Stocks and Hayward developed a haptic system HaptiMol ISAS [18]. It allows the user to interact with the biomolecular solvent accessible surface through the haptic device. A navigation cube is used to visualize the explored surface region, and the cube can be automatically scaled to fit the workspace of haptic device. The cube approach allows choosing a limited interaction area of very large molecules. In another approach for the rigid body molecular docking proposed by Subasi and Basoglan [19], the user can insert a rigid ligand molecule into the cavities of protein to search for binding cavity. Similarly to the cube approach, an Active Haptic Workspace (AHW) was implemented for the efficient haptic-based exploration of large protein-protein docking in high resolution. In the system, the user could feel a tunneling effect when the ligand molecule is pulled towards the binding cavity. In [20], an Interactive Global Docking (IGD) approach was presented. An immersive environment for docking interface with both visual and haptic rendering was implemented. The commercial Falcon haptic device from Novint Technologies was used to provide three degree-of-freedom force feedback. In [21], an Interactive Molecular Dynamics (IMD) system was implemented. A real-time force feedback based virtual reality system Steered Molecular Dynamics (SMD) [22] was developed for dynamic simulations of bimolecular interaction. Project of CoRSAIRe [23] is an example of a multisensory virtual reality system designed for a study of protein-protein docking. To create an immersive virtual environment, the visual, audio and 6-DOF haptic interfaces were combined to enhance the process of exploration.

Besides the rigid molecular modeling, some new approaches use flexible models to simulate molecular docking process. Daunay and Micaelli [24] developed a new molecular docking system which enables the feeling of both force and torque. The system provides haptic feedback for a flexible ligand-protein docking. However, the system has limitations on the size of protein molecules.

Haptic-enable web-based molecular docking is a new research direction in development of molecular docking simulation. In [25], Davies implemented a prototype of Molecular Visualiser (MV) system with Web3D standards adding an extension to support haptic interaction. MV provides the following features: visualizations of molecular systems, visualization of potential energy surfaces, and implementation of wavepacket dynamics. The system can run in a web browser using VRML, or be delivered to a virtual environment in which haptic properties are assigned based on the molecular dynamics of the system. Applications of MV for both research and teaching are also discussed. The authors mainly focused on the visualization of the molecular models and did not study molecular docking problem. Liu and Sourin [26] proposed a functional approach for modeling geometry of objects. The function-based objects were added into VRML. The user is able to define function of any shape with implicit functions. Later, Wei et al [27-28] extended the system proposed in [26] by incorporating haptic based features to new FVRML nodes. A new density node was proposed for haptic implementation. It allows exploring an electrostatic force of molecule with a probe in VRML.

In the previous works [1-2], we described our work on haptic-based visual molecular docking targeting on the research of helix-helix docking. In [2], we proposed an e-learning scenario with our system. In paper [29], we described the system interface and further development of a prototype of biomolecular docking system Haptic-based Molecular Docking (HMolDock). In this paper, we describe our system implementation with torque force that allows the user having more real experience in the molecular docking.

III. BASIC CONCEPTS AND ALGORITHM DESCRIPTION

We developed the prototype of biomolecular docking system HMolDock using the haptic device PHANTOM 1.5/6DOF. A Protein Data Bank [30] format file of molecular structure is used as an input of the molecular model. Atom coordinate is got from the input PDB files, the radius, position and the correspondent colour are also determined based on the atom type and its belonging residue which is extracted from PDB data. An interaction force including torque force between ligand and receptor are calculated and displayed in real time, so that the user could feel an attractive/repulsive force and rotation torque through the 6-DOF haptic device simultaneously.

A. Force Calculation

In calculation of interaction forces between ligand and receptor, we use the method of Lennard-Jones potential calculation which has been considered as the most important factor in tansmembrane α-helix interaction [31]. The interaction forces between molecules are well approximated by LJ potential which changes according to the distance between molecules. Therefore, a potential energy can be used to represent the interactions between two large molecules. Assume that there are $M$ atoms in receptor and $N$ atoms in ligand, the LJ potential between two molecules is shown below:
where $\varepsilon_{ij}$ and $\sigma_{ij}$ are LJ parameters for atom $i$ in receptor and atom $j$ in ligand, $r_{ij}$ is the distance between the atom pair.

Furthermore, the force function is derived as follows:

$$F = \nabla V(r) = d(V(r)\hat{r})/dr$$
$$= \sum_{i=0}^{M} \sum_{j=1}^{N} 24\varepsilon_{ij} [2(\sigma_{ij}^{12}/r_{ij}^{13}) - (\sigma_{ij}^{6}/r_{ij}^{7})] \hat{r}$$

where $\hat{r}$ is the distance unit vector. The $(1/r_{ij})^{13}$ term describes repulsion force, and the $(1/r_{ij})^{7}$ term describes attraction force. Depending on the distance between two molecules, these two opposite force factors play the dominate role alternatively.

There are many different force field models that can be used to simulate proteins and other molecules. The model used and described in here is OPLS-aa [32-34] which is parameterized for small organic molecules in protein simulation.

For the homo-atomic pairs, there are published LJ parameters available (i.e. [35] for OPLS-aa). The interaction of hetero-atomic pairs, the effective values of $\sigma$ and $\varepsilon$ are calculated from those for the homo-atomic pairs. This way of calculation is called mixing rule. OPLS-aa uses the same non-bonded functional forms as AMBER [36], and the Lennard-Jones terms between unlike atoms are computed using the mixing rule [37].

$$\sigma_{ij} = \sqrt{\sigma_i \sigma_j}$$
$$\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}$$

B. Torque Calculation

Most of the haptic rendering algorithms for molecular docking are based on three degree-of-freedom haptic devices which can only simulate force effects by moving along three coordinates. However, with 6-DOF haptic devices, the torque feedback of ligand can be calculated to produce the torque effects which could add rotation force around 3 axes in virtual environment.

For some previous torque calculations, the torque is only calculated around the position of haptic device’s attachment point which is set to be the closest atom to the ligand’s center of mass [38]. In our algorithm, we chose a more flexible way when the torque force can be calculated at any surface position of the ligand. As long as a haptic interface point (HIP) is attached to the ligand and the docking process started, the position of HIP is stored and updated to calculate the torque feedback. In this way, the user has more freedom in manipulation of the ligand. Especially in e-leaning, the users could have a better understanding of interactions between molecules with changing position of HIP.

The calculation of the torque force requires atom forces derived from (2) and the position of the haptic interface point $X_{HIP}$ on the ligand as well. Like the computation of force, the torque feedback is the sum of all torque effects from atom pairs between ligand and receptor. The haptic torque $T$ is calculated as follows:

$$T = \sum_{j=0}^{M} [(x_j - x_{HIP}) \times \sum_{i=0}^{M} F_i]$$

Where $x_j$ is the position of ligand atom $j$, $x_{HIP}$ is the position of contact point between haptic interface point and ligand. For the specific ligand atom $j$, $\sum_{i=0}^{M} F_i$ represents the interaction force between one ligand atom and all atoms of the receptor. The torque is calculated by the cross product between a force vector and a displacement vector (vector from the point that torque is measured to the point where Van der Waals force is applied).

C. Stability of Haptic Rendering

The force and torque are calculated from the sum of interaction forces of all possible atom pairs between two molecules. It is well known that this force is extremely sensitive to the distance. There would be a sudden change on the force direction and magnitude when the Van der Waals force changes from attraction to repulsion. This sharp change of the force vector can cause sudden jump effect in successive force and torque frames of haptic devices.

To achieve the smooth Van der Waals force, we use a linear smoothing method similar with [39] to avoid this kicking phenomenon which is caused by the sudden change of force display during molecular docking process. First, we set a maximum step size $F_{sup}$ for the successive force magnitudes. To achieve a smooth haptic update, the setting of $F_{sup}$ depends on the type of haptic device and computer configuration. The force calculated in a previous frame is $F_{i-1}$ and the current force is set to be $F_i$. The kicking problem is often happened when $F_i > F_{i-1}$. Due to the high update rate of haptic pipeline, a simple algorithm is used for the force display. When $F_i - F_{i-1} > 2F_{sup}$, the current force is set to $F_{i-1} + F_{sup}$. When $2F_{sup} > F_i - F_{i-1} > F_{sup}$, the current force is set to $F_{i-1} + F_{sup} / 2$. When $F_{sup} > F_i - F_{i-1}$, the force does not change. In addition, this algorithm is also used for the rendering of torque update. Although there are some other methods that could be used to improve stability of the haptic rendering, this method is proved to be computationally efficient.

The purpose of bimolecular docking is to find the position with the minimal potential energy. However, in practice, this position is hard to be captured manually since there is a great change in the force magnitude from attraction force to repulsion force. As a result, the user with a haptic device is hard to stay in this minimal energy position in practice.

To solve the problem of potential unstable factor and to produce an accurate manipulation, we set a zero area when the energy of molecular docking force is very small, as it is shown in the red area of Fig. 1. Therefore, the user can have
a stable control of ligand and maintain it in the position of the minimal energy area. Otherwise, there would be an obvious vibration around this area.

IV. SYSTEM IMPLEMENTATION AND PERFORMANCE

In this section, we describe the HMolDock system and the results of molecular docking interaction. To display the force and torque feedback, the PHANROM Premium 1.5/6DOF designed by SensAble Technologies is used in our system.

A. Implementation

The proposed haptic force-torque rendering algorithm has been implemented in our prototype HMolDock. The system is developed and tested on a dual 1.86GHz CPU workstation using OpenHaptics® Toolkit, OpenGL® library and Visual C++ programming language. Fig. 2 shows the set-up of the HMolDock system with 6-DOF force-torque feedback haptic device in the laboratory.

Although there are different file formats for molecular structures, we use a Protein Data Bank (PDB) format for the input. Two molecules could be visualized on the screen as shown in Fig. 2. The user could assign a haptic interface point to one of the molecules and move this molecule towards/around of another one to feel both force and torque feedback around three axes.

The haptic rendering pipeline mainly consists of molecule transformation, force and torque calculation, and stable force algorithm implementation. An overall structure of haptic rendering pipeline for bimolecular docking process is shown in Fig. 3.

Figure 1. The zero area (in red) is set when the potential energy approximates to zero, and the force changes from attraction to repulsion.

Figure 2. HMolDock system with PHANToM 6-DOF haptic device.

Figure 3. An overall structure of the haptic rendering pipeline with force-torque feedback.
optimized by the stable algorithm to display continuous and smooth force-torque feedback to the user.

B. System Performance

Fig. 4 shows a bimolecular docking process between one αIIb helix (with 154 atoms) and one designed antibody-like complementary peptide anti-αIIb (with 266 atoms). The coordinate grid is used to help the user to improve the accuracy of manipulation in 3D environment. After molecules are loaded into the system, the user can assign a haptic interface point to probe and grab the ligand which can be moved towards/around the receptor. The position of contact point between haptic probe and ligand is used to calculate the torque force caused by all atoms pairs between ligand and receptor. The resulting attraction/repulsion forces and rotation torques forces can be displayed through the 6-DOF haptic device. Therefore, the molecule can be selected by the haptic mouse and moved around to let the user ‘feel’ the force-torque feedback in our bimolecular system.

Values of force and torque magnitudes are shown on the right side of the screen to help the user to find the optimum docking position. In addition, the force direction and magnitude are visualized as a yellow vector, and the cyan vector indicates the change of torque vector. Here, the direction and length of the arrow indicates the attraction/repulsion force and its magnitude. Fig. 4(a) shows an attraction force between two separated molecules. As the distance becomes smaller, the repulsion force will appear and increase rapidly. Fig. 4(b) shows the force and torque directions and magnitudes when two molecules contact with each other. Both directions of force and torque change to the opposite, and the increased magnitudes can be read from the value shown on the right side of the screen.

With the intuitive vector representation and force-torque feedback, the user can experience more realistic force feeling during the docking process and analyze the optimal positions of minimal potential energy.

C. Analysis

Fig. 5 shows both force response and torque response in one molecular docking process. During this process, the haptic device manipulates the ligand approach to the receptor from a far apart distance to a contact status. We divide this molecular docking process into the following three time intervals:

- $T_0 < T < T_1$ (Separate): two molecules are far apart, the force and torque magnitudes are very weak.
- $T_1 < T < T_2$ (Approach): two molecules are separated with a limited distance.
- $T_2 < T < T_3$ (Contact): the ligand contacts with receptor, the repulsion force increases greatly.

As shown in Fig. 5, both Van der Waals force magnitude and torque magnitude change according to the distance between two molecules with the same trend. In addition, the force magnitude is greater and more sensitive than the torque magnitude in the process of molecular docking. Through our biomolecular docking system HMolDock, the force and torque change from attraction to repulsion can be directly experienced by the user while performing drug design or molecular docking simulation. Therefore, the optimum docking position can be found by the intuitive haptic feeling instead of expensive computation of docking algorithms.
Figure 5. Force and torque magnitude in a molecular docking process.

V. CONCLUSION AND FUTURE WORK

In this paper, first, we introduced research background of molecular docking and reviewed visual and haptic based molecular docking systems. Most of the systems use devices with three degree-of-freedom that lack of providing the user "real" feeling of molecular interaction with force-torque feedback during the molecular docking. In this paper, we proposed and described the haptic rendering algorithm with torque force for molecular docking system. To provide an additional flexibility of the torque display in the molecular docking process, the user can change the attach position where to apply device to move a ligand. Also we introduced the stability method to provide smooth force and torque feedback.

Currently, the system is implemented as a standalone application. There are many directions for future research. We are planning to realize the biomolecular docking in collaborative virtual environments and implement the haptic rendering for more complex molecular models.

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